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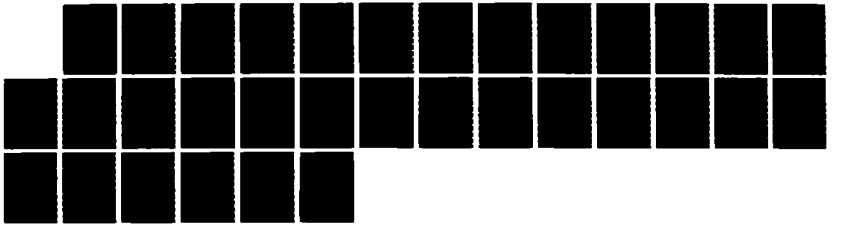

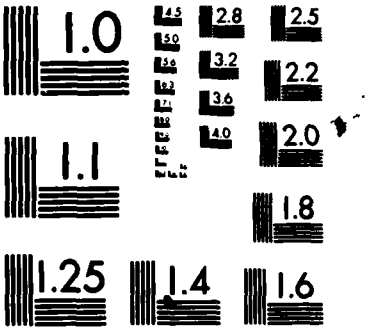

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GENETIC MARKERS OF HOST RESISTANCE AND/OR SUSCEPTIBILITY TO THE LETHAL EFFECTS OF RADIATION AND COMBINED RADIATION-BURN INJURIES

State University of New York at Stony Brook
Department of Surgery, School of Medicine
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1 December 1985

Technical Report

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The results suggest that strains of rats of differing genetic backgrounds differ widely in their susceptibility to the lethal effects of ionizing radiation. Just as has been observed in the same species with thermal injury, the capacity of rats to withstand the lethal effects of irradiation appear to be governed by genetic factors. The 8 inbred and 2 randomly bred strains of rats tested could be grouped (on the basis of $LD_{50/30}$ determinations) into three categories, ranging from highly susceptible (ACI and BN) strains to 5 strains of intermediate susceptibility (W, OM SD, LEW DA) and to 3 highly resistant, i.e., least susceptible strains (WF, F344, BUF). As observed earlier with thermal injury, females of the same strain were more susceptible to the lethal effects of radiation; this effect was particularly marked in pigmented strains. Two inbred pigmented strains bearing train h^i/h^i (homozygous recessive "Irish" gene for coat color) were the most susceptible to radiation vis-a-vis 7 other albino strains and one other pigmented strain (DA), which lacks the h^i/h^i gene. There may therefore be an association between skin pigmentation and/or coat color and the genetic determinants of

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19. ABSTRACT (Continued)

susceptibility to the lethal effects of radiation. Comparison of the susceptibility of the same strains to the lethal effects of severe thermal injury provides no evidence of a parallel influence of skin pigmentation or coat color upon such susceptibility. While one pigmented strain (ACI) was most highly susceptible, the other pigmented strain (BN) was in the least susceptible category. The evidence also points to the probability that MHC factors are not involved in conditioning host susceptibility to severe radiation injury. When comparing the effects of thermal injury and radiation, the results have identified (a) one strain (ACI, which is pigmented and bears the h^i/h^i trait) that is highly susceptible to both thermal and radiation injury; (b) one strain that is highly resistant to both types of injury (BUF, which is albino); (c) one strain which is highly susceptible to thermal injury but highly resistant to radiation (F344, which is albino); and (d) one strain which is highly resistant to thermal injury, but highly susceptible to radiation (BN, which is pigmented, and bears train h^i/h^i). These characteristics (1. skin pigmentation, 2. coat color, 3. susceptibility to thermal injury; 4. susceptibility to radiation) may be amenable to genetic analysis in breeding experiments in these four species, where back-cross studies may permit separation of skin color and the h^i trait, in order to determine which of these characteristics is directly associated with susceptibility to radiation. The possible separability of host susceptibility to thermal injury and to radiation will be of singular usefulness in developing a genetic model of host reactivity to these modalities.

The data provide an explanation for the additive effects of burns and radiation described in earlier studies since such studies were performed in male albino rats of undefined genetic backgrounds. The identification in the current study of inbred rat strains which differ exquisitely in susceptibility to either burns or radiation may provide an altogether new approach to the genetic analysis of the factors which control host responses to either injury. The possible association of genetically separable components with high susceptibility to radiation injury (skin pigmentation, coat color) is of particular interest. Further studies may provide an approach to prospective identification of individuals who are susceptible to either injury, and may be of particular importance from a military, civil defense and space research standpoint.

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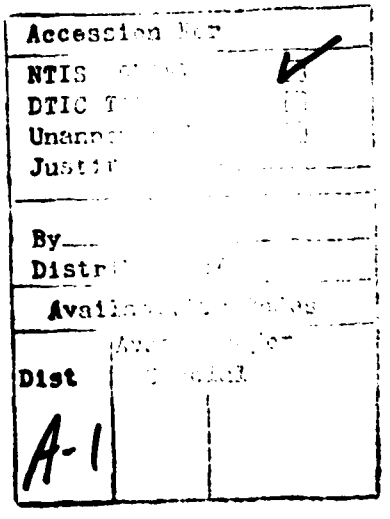

SECTION 1

INTRODUCTION

Previous studies in this laboratory have shown that the broad variations in host resistance and mortality observed after severe thermal injury are under genetic control, and that the specific genetic background of the injured host can provide a predictive index of the recipient's course after injury. In these studies, significant variations occurred in the response of outbred and inbred strains of rats to exposure to a standard 40% body surface area full-thickness skin burn. Some strains were highly susceptible to injury (95% to 100% mortality); other strains showed intermediate susceptibilty (45% to 65% mortality), while others were highly resistant (4% to 14% mortality) to the same injury.

The documented additive effects of thermal injury and ionizing radiation have raised the possibility that host resistance and/or susceptibility to ionizing radiation might be amenable to genetic analysis in the same manner as was observed in severe burns. It also appeared of interest to ascertain whether the genetic factor(s) (if any) controlling host susceptibility to ionizing radiation were closely linked to or identical with the genetic factor(s) identified in the control of the host's natural resistance or susceptibility to the lethal effects of severe thermal injury. Specifically, the current project proposes to identify and analyze genetic parameters in determining host resistance and/or susceptibility to ionizing radiation, utilizing a standard end-point of mortality following graduated dose and time-controlled exposure to ionizing radiation. The first portion of the project involves the selection of a number of strains of inbred and outbred rats, and their exposure to ionizing radiation under the same conditions, followed by a determination of the mortality observed in each strain, in association with detailed necropsy and microbiological studies in each animal succumbing to the effects of ionizing radiation.

SECTION 2

MATERIALS AND METHODS

The experimental animals were male and female rats from 10 different strains, including 7 inbred strains {ACI; Brown-Norwegian (BN); Buffalo (BUF); Dark Agouti (DA); Fisher (F344); Lewis; Wistar-Furth (WF)}, and 3 outbred strains {Osborne-Mendel (OM); Sprague-Dawley (SD) and Wistar (WI)}. The animals were obtained from the World Reference Center for Rat Immunogenetics, Department of Pathology, University of Pittsburgh School of Medicine, and from commercial breeding sources, including Microbiological Associates (Walkersville, Md.), Camm Research (Wayne, N.J.), the Charles River Laboratories (Wilmington, Maine), the Harlan-Sprague Dawley Laboratories (Indianapolis, In), the Taconic Farms (Taconic, N.Y.) and the Trudeau Institute (Saranac Lake, N.Y.) (Table I).

All animals were acclimatized for 3 weeks in the Division of Animal Laboratory Resources at S.U.N.Y. at Stony Brook before exposure to radiation. The animals were housed in individual cages, and kept in a controlled environment room maintained at 22-25°C ± 1°C and 40% humidity. A standard Purina pellet diet, and water, were provided ad libitum.

Host exposure to ionizing radiation was provided with a Gammacell 40 Cesium-137 irradiation unit (Atomic Energy of Canada, Ltd., Ottawa, Canada), which provides a highly reliable and reproducible source of uniform total body gamma irradiation for small animals, under controlled rate and dosage conditions. This unit includes an air compressor with reservoir tank, as a source of filtered and regulated air for ventilation purposes. After exposure to a predetermined dose of total body irradiation, the rats were returned to the same controlled environment, and were followed closely for the following 30 days. During this time, all animals were observed twice daily, and cumulative mortalities in each experimental group were determined. Necropsy and microbiological studies were performed in succumbing animals. The statistical significance of the mortality data was analyzed by the nonlinear method of least squares. Particular attention was paid to evidence of differences in susceptibility to irradiation in inbred rat strains of differing genetic backgrounds. Evidence was also sought for the possible existence of sex-linked determinants which might also exert an influence upon the results. For this purpose, the results observed in parallel groups of male and female rats of the same strain exposed to the same dose of irradiation were compared in systematic fashion in each of the strains studied.

The first goal of the study was to establish the appropriate dose of irradiation capable of yielding a 50% mortality rate within 30 days within each strain of rats under study ($LD_{50/30}$). For this purpose, groups of male and of female rats from each strain were exposed to radiation doses ranging from 600 to 1,200 r in the Gammacell 40 unit, in various incremental doses. The initial test doses selected were based on earlier data in some of the strains, available in the literature, in order to identify rapidly the optimum informative dose range for each strain. A total of 1,816 rats from 8 inbred, and 2 outbred strains has been studied, and the results are outlined in this Report. The scope and timing of the experiments and the number of animals included in each group were conditioned significantly by the available supply of many of these strains from commercial sources, and the occurrence this year of a severe

epizootic infection in the Pittsburgh Rat Vivarium. In spite of these limiting factors, work has now been completed in all strains.

For the necropsy and microbiological studies, each animal succumbing to the effects of ionizing radiation was first weighed and examined grossly. All animals were placed after death in a sterile plastic envelope which was sealed and stored at 4°C until necropsy. The average time elapsing between death and necropsy was generally 12 hrs. Following a search for arthropods, swabs of the oropharynx were obtained for bacterial culture, and, after cleansing the animal, a ventral midline incision was made from mandible to anus, and the skin was reflected from the underlying muscles. The trachea was freed by blunt dissection, and was partially transected. The tip of a sterile Pasteur pipette, containing 0.5 ml of sterile water was inserted into the trachea, and water was flushed gently into the lungs and reaspirated. These bronchial washings were inoculated on blood agar plates and any microbial colonies found at 18-24 hrs were subcultured. Similar nasopharyngeal washings were obtained and cultured. The entire ventral body wall overlying the abdominal and thoracic cavities was then excised, and the viscera were examined. Using a red-heated spatula, the liver surface was seared, and the burned area was excised with a scalpel. A sterile cotton swab was then rotated in the exposed liver tissue. The swab was also cultured in blood agar. The entire spleen was grasped with sterile forceps and freed of omental and vascular attachments. Specimens were saved for histology and the remainder was emulsified in sterile water. The emulsion was cultured in blood agar, and any 18 hr microbial growth was subcultured in standard fashion.

The ribs were broken dorsally, and a blood sample was aspirated directly from the right heart. The aspirate was cultured on blood agar plates, and any bacterial colonies isolated at 18 hrs were subcultured. The thoracic organs were then removed en bloc. The organs were examined, and the left lung was removed for histologic study. The intestinal loops were examined, and a 2 cm length of distal ileum was dissected free. A drop of ileal contents was examined microscopically, and ileal tissue was placed in formalin for histologic study. The cecum was dissected free and examined for helminths. Where indicated, specimens of duodenum, jejunum, ileum, and colon were excised for histologic study. The kidneys and liver were examined and sections were taken for histologic study. The colon was transected at the rectum, and a few fecal pellets were extruded for study of the enteric flora. The urinary bladder was transected and checked for helminths. All swabs, washings and tissue specimens underwent careful microbiological analysis, using standard culture plates and media (Analytab Products, Inc., South Plainfield, N.J. - API 20E System; and American Scientific Products, Edison, N.J. - NF 180 System).

SECTION 3

RESULTS

The individual strains and numbers of rats used in this study are outlined in Table I. Ten different strains of rats, including 8 inbred strains of rats and 2 random bred strains (Sprague-Dawley and Wistar) were selected for this study. As shown in Table I, the inbred strains of rats were characterized by a spectrum of Rt.1 haplotypes, including a, b, 1, n, and u (Rt.1 is the main histocompatibility complex (MHC) in the rat species). A total of 1,815 rats, including 905 males and 911 females, obtained from 6 different sources has been studied.

In order to ascertain the $LD_{50/30}$ (in r.) of total body irradiation, each strain of rats was exposed to a range of total body irradiation extending from 600 to 1,200 r., as shown in Table II. Informative results have now been obtained in all strains, and confirmatory studies have highlighted the reproducibility of the reported results. The $LD_{50/30}$ was calculated statistically on the basis of regression analysis of the linear portion of the dose response curves provided by the results outlined in Table II. For the purposes of this study, individual groups of male and female rats of each strain, including at least 8-12 members in each group, were exposed to a predetermined dose of irradiation under standardized condition, and were then observed for the following 30 days. As shown in Table III, the inbred ACI and BN rats were the two strains most susceptible to the lethal effects of irradiation. The comparative degree of susceptibility was determined on the basis of calculated $LD_{50/30}$ of radiation under standardized conditions in these strains. For example, a strain such as ACI, in which the radiation $LD_{50/30}$ in males was 662 r was considered more susceptible to irradiation than the BUF strain, where the $LD_{50/30}$ was 864 r. Generally similar results were noted in female rats. As shown in Table III the strains fell into a most susceptible group (ACI and BN), an intermediate group (W, OM, SD, LEW and DA), and a least susceptible group of strains, which included the F-344, WF and BUF rats. The differences in strain susceptibility to irradiation were significant at levels of $P<0.005-0.001$ in males as well as females. Taken together, the differential susceptibility of various different inbred strains of rats to the lethal effects of radiation injury are in harmony with the conclusion that such susceptibility in parallel with earlier studies of thermal injury may also be under genetic control. Further study of congenic strains will be required, however, to confirm this possibility.

Earlier data outlined in an Interim Progress Report submitted to the Defense Nuclear Agency on 1 April 1985 alluded to a possibility of differences in host susceptibility to radiation during the growth and plateau phases of development within the same strain. These data were based upon studies in a limited group of rats, and have not been confirmed when the series of animals tested was enlarged.

There have, however, been several additional findings which appear to be of special interest. The first is that, in parallel with the observations made in the course of earlier studies of host susceptibility to thermal injury, females are significantly more susceptible to the effects of the same dose of irradiation than males of the same strain. This finding was particularly evident in the more highly susceptible (ACI, BN) and in the pigmented strains

(ACI, BN, DA) and in one albino strain (LEW) ($P<0.001$) (Table III). The data outlined in Table III also point to the probability that products of the rat MHC do not have an influence upon host susceptibility to radiation. For example, the most highly susceptible strain (ACI) bears the MHC genotype $Rt.1^a$, and shares this trait with the intermediate-susceptibility strain DA, while the highly resistant WF strain bears $Rt1^u$, in common with the intermediate susceptibility strain OM.

Table IV provides a correlation between levels of host susceptibility to radiation injury and the skin pigmentation and coat color of the rat strains examined. It appears to be of particular interest that the two most susceptible strains (ACI, BN) are pigmented, although the other pigmented strain (DA) is only of intermediate susceptibility. Further genotyping analysis of these strains indicates, however, that, while the ACI and BN strains share the h^i/h^i (hooded Irish recessive gene), and a/a, b/b, C/C, h^i/h^i, respectively, the third pigmented strain, DA lacks this particular trait (as shown in Table IV, the DA genotype is A/A, B/B, C/C). These observations raise the very intriguing possibility that genetic determinants coding for skin pigmentation and/or coat color may also be of importance in determining the fate of a given host upon exposure to radiation. Such a possibility may provide a uniquely valuable approach to further genetic study of the genetics of host susceptibility to radiation injury.

Table IV also provides a comparison between the rankings of host susceptibility to thermal injury and radiation injury. The two strains found to be most susceptible to the mortality of severe burns were ACI and F-344, and the least susceptible were BN and BUF. In contrast, the two strains most susceptible to radiation were ACI and BN, and the two least susceptible strains were F-344 and BUF. These four inbred strains of rats may therefore provide a valuable opportunity to separate by selective breeding the genetic determinants implicated in host susceptibility to thermal injury on the one hand, and to radiation on the other.

NECROPSY AND MICROBIOLOGICAL STUDIES

Rats dying after irradiation underwent necropsy examination and dissection, with microscopic study where indicated, as well as microbiologic study of 6 body locations, and bone marrow cytologic examinations. The results were analyzed in terms of early, middle, and late periods, corresponding to death within 1-7, 8-14, and 15-30 days, respectively, after irradiation.

From the standpoint of gross lesions and clinical signs, the most prominent findings in the 1-7 and 8-14 day groups were dehydration, sanguineous nasal and ocular discharges, and diarrhea. These signs were less evident in the 15-21 day group. Microbiologic results were determined in each of 6 locations: (1) oropharynx, (2) tracheopulmonary airways, (3) cardiac blood, (4) liver, (5) spleen and (6) nasopharynx. The results were somewhat obscured by one ubiquitous microorganism, Proteus vulgaris (Pv), which occurred in 100% of all cultured animals. Pseudomonas aeruginosa (PA) could be identified, however, where present, by interpreting the presence of other cytochrome oxidase (+) forms as representing PA. Pv was common in oropharyngeal isolates along with PA, and a variety of coliforms, mainly Escherichia coli (EC). The results were similar in the nasopharynx and tracheopulmonary airways; here, also, PA predominated in 90-95% of the animals in the early, middle or late

death groups. Similar data were obtained with cardiac blood, liver and spleen. All organs were infected with PA, and Py was a frequent contaminant as well.

Microscopic study showed diffuse centrolobular hepatocellular degeneration in 75-100% of all rats in the early and middle death groups. Almost all of the examined kidneys (90-100%) showed a moderate primary tubular injury and degeneration of the ascending and descending loops of Henle, in cortex and medulla. The adrenal glands appeared grossly and microscopically normal. Three levels of intestine (duodenum, ileum, colon) were examined routinely in rats from the early, middle and late death groups. The tissues were affected by radiation, with a progression from essentially normal specimens to necrosis of the tips of the villi, and to mucosal necrosis and sloughing. The lesions were most severe in the duodenum, intermediate in the ileum, and mildest in the colon. The lungs were also affected; the primary target was the airway epithelium, especially in the bronchi and bronchioles. Different areas of the same lobe, or even of the same bronchus, were noted to develop either hyperplasia and redundancy of the epithelium, or necrosis and sloughing of the epithelium, leaving ulcerated surfaces. Metaplasia to a thin, cuboidal epithelium occurred often in these areas. The primary epithelial lesions were associated with accumulation of edema fluid and/or blood in the lumen of the affected bronchus. This, in turn, produced sanguineous nasal and occular discharges. The lesions occurred in all rats studied.

Irradiation had a severe effect upon the bone marrow (BM). The mean cellularity of the BM was 1.75 in the early (1-5 day deaths) group; it decreased to 1.65 in the intermediate (8-14 day deaths), and was 1.3 in the late deaths group. Bone marrow repair in the late group was particularly impaired (as evidenced by lack of cellular regeneration). As regards body weight, the animals lost 30-40% of their baseline body weight during the 2 weeks following exposure to ionizing radiation. The chief determinant of the weight loss and associated dehydration appeared to be the radiation- induced interference with gastrointestinal epithelial function.

Pathological and microbiological observations were consistent in all rat strains studied. The primary targets and most severe lesions in the early deaths group were the tubular epithelium of the gastrointestinal tract, with particular severity in the duodenum; the respiratory tract was also affected. Subsequent deaths could be ascribed more prominently to failure of bone marrow function.

SECTION 4

DISCUSSION

The results submitted in this report suggest that, under the same experimental conditions, strains of rats of differing genetic backgrounds differ widely in their susceptibility to the lethal effects of ionizing radiation. Just as has been observed in the same species with severe thermal injury, the capacity of rats to withstand the lethal effects of irradiation appear to be governed by genetic factors. The 8 inbred and 2 randomly bred strains of rats tested could be grouped (on the basis of $LD_{50/30}$ determinations) into three categories, ranging from highly susceptible (ACI and BN) strains to 5 strains of intermediate susceptibility (W, OM SD, LEW DA) and to 3 highly resistant (i.e., least susceptible) strains (WF, F344, BUF). As observed earlier with thermal injury, females of the same strain were more susceptible to the lethal effects of radiation; this effect was particularly marked in the pigmented strains. It seemed to be of particular interest that the two inbred pigmented strains bearing trait h^i/h^i (homozygous recessive "Irish" gene for coat color) were the two strains most susceptible to radiation injury, vis-a-vis, 7 other albino strains and one other pigmented strain (DA), which lacks the h^i/h^i gene. There may therefore be an association between skin pigmentation and/or coat color, and the genetic determinants of host susceptibility to the lethal effects of radiation. The evidence does not, at this time, support an association between products of the rat MHC and host susceptibility to irradiation.

Analysis of these results, and a comparison of the susceptibility of the same strains to the lethal effects of severe thermal injury provides no evidence of a parallel influence of skin pigmentation or coat color upon such susceptibility. While one pigmented strain (ACI) was most highly susceptible (Table IV), the other pigmented strain (BN) was in the least susceptible category. The evidence also points to the probability that MHC factors are not involved in conditioning host susceptibility to severe thermal injury. When comparing the effects of thermal injury and of radiation in the rat strains studied for both modalities, it appears that the results have identified (a) one strain (ACI, which is pigmented and bears the h^i/h^i trait) that is highly susceptible to both thermal and radiation injury; (b) one strain that is highly resistant to both types of injury (BUF, which is albino); (c) one strain which is highly susceptible to thermal injury but highly resistant to radiation (F344, which is albino); and (d) one strain which is highly resistant to thermal injury, but highly susceptible to radiation (BN, which is pigmented, and bears trait h^i/h^i). These characteristics (1. skin pigmentation, 2. coat color, 3. susceptibility to thermal injury; 4. susceptibility to radiation) may therefore be amenable to genetic analysis in specific breeding experiments in these four species, where back-cross studies may permit a separation of skin color and the h^i trait, in order to determine which of these characteristics is directly associated with host susceptibility to radiation. The possible separability of host susceptibility to thermal injury and to radiation will also be of singular usefulness in developing a genetic model of host reactivity to these two modalities.

With the exceptions noted (i.e., F344 and BN strains), there is an interesting paralellism between the hierarchy of strain susceptibility to thermal and radiation injury. In both instances, ACI rats were the most susceptible, and BUF rats were the least susceptible; WF rats were also in the

least susceptible category (Table IV). The W, LEW, OM and SD strains were in the intermediate category for susceptibility in thermal as well as radiation injury. This category, as might have been anticipated included the two outbred strains tested (W, SD) in both studies. Taken together, these data may provide an explanation for the additive effects of burns and radiation described by other authors in earlier studies since such studies were performed in male albino rats of undefined genetic backgrounds. The identification in the current study of inbred rat strains which differ exquisitely in their susceptibility to either burns or radiation may provide an altogether new approach to the genetic analysis of the factors which control host responses to either form of injury. The possible association of genetically separable components associated with high susceptibility to radiation injury (skin pigmentation, coat color) is of particular interest in this regard. The possibility that such studies may provide an eventual approach to the prospective identification of those individuals who may be susceptible or resistant to either form of injury, may be of particular importance from a military, civil defense and space research standpoint.

The results of necropsy and microbiological studies suggest that, regardless of the level of host susceptibility to ionizing radiation, the end process leading to death was essentially similar in all strains. In keeping with earlier observations, the loci minore resistantiae in animals succumbing to irradiation shortly after exposure (early deaths) were the gastrointestinal and respiratory tracts. The principal cause of death appears related at this time to the severity of gastrointestinal injury, with massive diarrhea, fluid loss and resulting hypovolemia and shock. Most animals succumbing during this early phase were either exposed to extremely high doses of radiation (900-1,200 r.) and/or belonged to the most highly susceptible strains, such as ACI and BN. In the late post-radiation group, the principal cause of death was bone marrow dysfunction and/or aplasia. The pathological and physiological findings were generally uniform in all rat strains studied. The severity of the lesions and the acutal time of death (early, intermediate, or late) were generally a function of the radiation dose employed, the level of strain specific susceptibility to radiation, and the sex, skin pigmentation and coat color of the animal.

The investigators believe that some important new information regarding the role of genetic factor(s) conditioning host susceptibility to the lethal effects of radiation injury has been developed in the course of the studies performed during this contract period. A number of intriguing new potential avenues of exploration of the genetics of host susceptibility to radiation and to burn injury have been opened. The experiments to be performed in further explorations of these approaches involve breeding of special animal lines (backcrosses, congenic lines, etc.) for which this team enjoys the unique facilities of the World Reference Center Vivarium for Rat Histocompatibility Genetics, at the University of Pittsburgh. It must be noted, however, that such studies are highly time-consuming, and that a minimum period of support for three years would be needed to establish a sound experimental design. A manuscript describing the results obtained thus far, and their biological implication is currently in preparation, and will be submitted for review and clearance by the Defense Nuclear Agency in due course, prior to submission for publication.

Table 1. Strains and numbers of rats used thus far in this study.

STRAIN	Rt1 HAPLOTYPE	NUMBER OF ANIMALS MALE	FEMALE	SOURCE*
ACI	a	96	96	HSD
BN	n	96	96	CR
BUF	b	48	48	HSD
F344	l	33	28	Pit
F344	l	48	48	CR
DA	a	40	36	TI
LEW	l	48	64	CR
OM	u	48	48	Ca
SD	Random Bred	96	96	TF
WI	Random Bred	184	181	CR
WF	u	168	170	HSD
TOTALS:		905	911	1816

*Ca: Camm Research, Wayne, New Jersey
CR: Charles River Labs, Wilmington, Mass.
HSD: Harlan Sprague-Dawley, Indianapolis, Indiana
Pit: University of Pittsburgh School of Medicine, Pittsburgh, Pa.
TF: Taconic Farms
TI: Trudeau Institute

Table 2. Strains of rats tested during the present reporting period and radiation dose ranges utilized.

Radiation Dose (r.)	ACI Males % Mort.	ACI Males # of Rats	ACI Females % Mort.	ACI Females #of Rats	BN Males % Mort.	BN Males # of Rats	BN Females % Mort.	BN Females # of Rats	WI Males % Mort.	WI Males # of Rats	WI Females % Mort.	WI Females # of Rats	OM Males % Mort.	OM Males # of Rats	OM Females %
1200									100	20/20	100	20/20			
1000									95	19/20	100	20/20			
975															
950															
925															
900															
875									100	12/12	100	12/12			
850									90	18/20	95	19/20			
825	100	12/12	100	12/12	100	12/12	100	12/12	81	26/32	100	32/32	75	9/12	83
800	100	12/12	100	12/12	100	12/12	100	12/12	63	20/32	67	20/30	75	9/12	50
775	100	12/12	100	12/12	83	10/12	100	12/12	40	8/20	65	13/20	25	3/12	33
750	100	12/12	83	10/12	100	12/12	92	11/12	40	8/20	55	11/20	0	0/12	33
725	83	10/12	100	12/12	50	4/8	100	8/8	50	4/8	43	3/7			
700	75	9/12	75	9/12	25	2/8	75	6/8							
675	58	7/12	67	8/12	13	1/8	75	6/8							
650	42	5/12	58	7/12	25	2/8	50	4/8							
625					0	0/8	38	3/8							
600					0	0/8	38	3/8							
575															
550															
525															
500															

:ilized.

OM			SD				LEW				DA				F344-PIT		
	Females		Males		Females		Males		Females		Males		Females		Males		F
of ts	% Mort.	# of Rats	% Mort.	# of Rats	% Mort.	# of Rats	% Mort.	# of Rats	% Mort.	# of Rats	% Mort.	# of Rats	% Mort.	# of Rats	% Mort.	# of Rats	% Mor
															60	6/10	92
			100	12/12	92	11/12											
			83	10/12	92	11/12			94	15/16	75	6/8			54	6/11	13
12	83	10/12	63	15/24	58	14/24	58	7/12	100	12/12	63	5/8	88	7/8	42	5/12	
12	50	6/12	38	9/24	67	16/24	42	5/12	92	11/12	38	3/8	63	5/8			
12	33	4/12	25	3/12	25	3/12	25	3/12	67	8/12							
12	33	4/12	17	2/12	25	3/12	0	0/12	58	7/12	0	0/8	38	3/8			

F344-PIT.			F344-CR				WF				BUF			
les	Females		Males		Females		Males		Females		Males		Female	
# of Rats	% Mort.	# of Rats	% Mort.	# of Rats	% Mort.	# of Rats	% Mort.	# of Rats	% Mort.	# of Rats	% Mort.	# of Rats	% Mort.	# R
							100	20/20	100	20/20				
							95	19/20	100	20/20				
							75	15/20	100	22/22	100	8/8	100	8
											75	6/8	100	8
6/10	92	11/12					80	16/20	65	13/20	50	4/8	88	7
											38	3/8	50	4
6/11	13	2/16					75	15/20	60	12/12				
5/12			0	0/12	0	0/12	25	3/12	42	5/12	50	4/8	38	3
			0	0/12	0	0/12	6	2/32	16	5/32	25	2/8	13	1
			17	2/12	0	0/12	17	2/12	17	2/12				
			0	0/12	0	0/12	8	1/12	9	1/12				

Table 3. Calculated LD/30 (r.) of total body irradiation in different strains of inbred and random-bred rats - relationship to MHC products, sex and skin pigmentation.

Strain	Source	Genetic Background And MHC Expression	Number of Rats Tested		*LD 50/30 Of Irradiation (in r)		Skin Pigmentation (Phenotype)	**Difference In Susceptibility In Females Of the Same Strain
			Male	Female	Male	Female		
ACI	HSD	Inbred Rt.1[a]	96	96	662	642	Pigmented Black body White Belly	P<0.025
BN	CR	Inbred Rt.1[n]	96	96	709	637	Pigmented All Brown	P<0.001
W	CR	Random Bred	184	181	745	731	Albino	N.S.
OM	CRL	Inbred Rt.1[u]	48	48	792	786	Albino	N.S.
SD	TF	Random Bred	96	96	805	795	Albino	N.S.
LEW	CR	Inbred Rt.1[l]	48	64	812	737	Albino	N.S.
DA	TI	Inbred Rt.1[a]	40	36	813	772	Pigmented "Agouti" Color	P<0.001
F-344	PIT	Inbred Rt.1[f]	33	28	849	(873)	Albino	N.S.
F-344	CR	Inbred Rt.1[n]	48	48	<825	<825	Albino	N.S.
W-F	HSD	Inbred Rt.1[u]	168	170	853	839	Albino	N.S.
BUF	HSD	Inbred Rt.1[b]	48	48	864	854	Albino	N.S.
10 Strains	Total # of Rats:		905	911				

* LD50/30 calculated on the basis of Regression Analysis of the linear portion of the dose response curves in Table II.

** Statistical comparison of mortality rates between male and female rats in each strain was performed using standard analysis of covariance, applied to the linear portion of the respective dose-response curves.

Table 4. Comparative susceptibility of male and female rats from different strains to the lethal effects of severe thermal injury and total body irradiation - relationship to skin pigmentation and coat color genotype.

Relationship of Rat Strain to Hierarchy of Host Susceptibility to Thermal Injury (From Most to Least Susceptible)		Skin Pigmentation And Coat Color In Each Strain		Relationship of Rat Strain to Hierarchy of Host Susceptibility to The Lethal Effects Of Radiation (From Most to Least Susceptible	Skin Pigmentation And Coat Color In Each Strain		Relationship of Rat Strain to Hierarchy of Host Susceptibility to the Lethal Effects of Radiation (From Most to Least Susceptible	Skin Pigmentation And Coat Color In Each Strain	
Male	Female	Phenotype	Genotype	Male Rats	Phenotype	Genotype	Female Rats	Phenotype	Genotype
ACI	ACI	Pigmented	a/a,B/B,C/C,h^i/h^i	ACI	Pigmented	a/a,B/B,C/C,h^i/h^i	ACI	Pigmented	a/a,B/B,C/C,h^i/h^i
F344	F344	Albino	a/a,c/c,h/h	BN	Pigmented	a/a,b/b,C/C,h^i/h^i	BN	Pigmented	a/a,b/b,C/C,h^i/h^i
W		Albino	Random Bred	W	Albino	Random Bred	W	Albino	Random Bred
LEW		Albino	a/a,b/b,h/h	OM	Albino	c/c	LEW	Albino	a/a,c/c,h/h
OM		Albino	c/c	SD	Albino	Random Bred	OM	Albino	c/c
SD		Albino	Random Bred	LEW	Albino	a/a,c/c,h/h	DA	Pigmented	A/A,B/B,C/C
WF	WF	Albino	c/c	DA	Pigmented	A/A,B/B,C/C	SD	Albino	Random Bred
BN	BN	Pigmented	a/a,b/b,C/C,h^i/h^i	F344	Albino	a/a,c/c,h/h	WF	Albino	c/c
BUF	BUF	Albino	c/c	WF	Albino	c/c	F344	Albino	a/a,c/c,h/h
				BUF	Albino	c/c	BUF	Albino	c/c

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